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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,775	01/04/2001	David J. Grainger	295.009US3	6351

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SCHWEGMAN, LUNDBERG & WOESSNER/NEORX
PO BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
10/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
request@slwip.com

Office Action Summary	Application No.	Applicant(s)	
	09/754,775	GRAINGER ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 3, 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *173-177,179-194,196-200,202,203,205,206,231 and 234* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *173-177,179-194,196-200,202,203,205,206,231 and 234* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 3, 2009 have been received and entered into the application.

Response to Arguments

Applicants' arguments filed August 3, 2009 have been fully considered but they are not persuasive. Applicants essentially argue that the Rule 132 Declaration enclosed herewith, executed by Dr. Grainger states that the prior to the effective filing date of the present application, compounds such as those with structural relatedness to tamoxifen, such as toremifene, were believed to elicit a beneficial effect as a result of their anti-estrogenic activity, and so it was understood that the target for those compounds was the estrogen receptor. Applicants further argue that the use of the female rodents to Sawada et al. implies that toremifene was being used because of its anti-estrogenic property; and that there is nothing in Sawada et al. that recognizes that certain compound that are structurally related to tamoxifen have a beneficial effect as result of their TGF-betas, e.g. TGF-beta1, elevating property and that this property is unrelated to the anti-estrogenic activity of compound. It was surprising that compounds within the scope of the claims in the present application would be useful to inhibit or treat a variety of cardiovascular or vascular indications, as they would have been expected to act as

anti-estrogen and that would have been expected to exacerbate the risk of cardiovascular disease. This is not persuasive because the Declaration has been carefully reviewed and considered. However, it is not persuasive because Applicants may have determine the mechanism of action of the compound that are structurally related to tamoxifen having elevating TGF-betas, e.g. TGF-beta1 activity, which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims. In this case, Grainger et al. teach that tamoxifen as well as its functional equivalents, analogs or derivatives thereof are a preferred TGF-beta activator/production stimulator. (page 4, lines 1-5). Grainger et al. teach that these TGF-beta activators and TGF-beta production stimulators are employed to maintain or increase vessel lumen diameter in a diseased or injured vessel of a mammal. (abstract). Therefore, the instantly claimed mechanism of action of the compound that are structurally related to tamoxifen having elevating TGF-betas, e.g. TGF-beta1 activity, is an unavoidably achieved by the earlier treatment of the same disorder related to the administration of the same tamoxifen related compounds in the patients disclosed by Grainger et al. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Applicants argue that Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. This is not found to be persuasive because the teaching of Sawada is clear that the effect of decrease in total cholesterol is resulted of orally administered NK622 (toremifene). Applicants' attention is drawn to second paragraph of abstract of Sawada where it states "This experiment yielded the following results… showed decreases in total cholesterol, phospholipid and total protein values in rats receiving 0.1mg/kg or more…". Applicant argues that Ito et al. provide no motivation to employ toremifene or any analogs thereof to treat any disorder other than one associated with autoreactive T cells. This is not found to be persuasive because Ito et al. clearly teach that toremifene is effective remedy for the treatment of blood vessel disease such as angitis which is evidenced by Schilling that it is a small vessel disease. Applicant's subject also having a comorbid diabetes would not change the useful teaching that toremifene is effective remedy for the treatment of blood vessel disease regardless of the subjects comorbid disease.

Applicants argue that Yang does not provide a reasonable expectation that an agent that elevates TGF-beta 1 level or a cytostatic dose of a compound of formula (I), would be useful to treat any disease, such as a cardiovascular or vascular indication characterized by a decrease lumen Diameter. This is not found to be persuasive because Yang teaches that toremifene is useful for treating osteoporosis because it induces human fetal fibroblast to secrete TGFb in absence of estrogen receptor. Yang

teaches that elevated serum levels of low density lipoprotein correlate with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction are noted in women with osteoporosis. Further, Yang teaches that transforming growth factor b, although commonly referred to as a single compound, "TGF b" is actually a family of molecules that now known to include at least three isoforms: TGF b-1, TGFb-2 and TGF-3. (column 3, lines 44-47). For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 173-177, 179-194, 196-200, 202,203,205,206, 231 and 234 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending Application No.

10/729,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending Application teaches an aspect of the claims in the instant application. For example, the method of claim 173 in the present application is similar to the method claimed in claim 153-173 utilizing same biological pathway comprising increasing the level of TGF-beta encompassing utilized same active agents. The copending application teaches the mechanisms of action or biological pathways presently claimed by Applicants and renders obvious the diseased claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 200, 202, 203, 205 and 206 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587B1 in view of Grainger et al. (WO 94/26303) of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent disclose and teach an aspect of the claims in the present application in view Grainger et al. Both sets of claims encompass administration of the same active agent (a structural analog of tamoxifen) to the same subject (a mammal at risk of or afflicted with a cardiovascular or vascular indication, e.g. atherosclerosis or in need of lowering serum cholesterol). Grainger et al. teach that atherosclerosis is a disease characterized by a reduced vessel lumen diameter. (abstract).

Therefore, any mechanism of action of increasing the level of TGF-beta is obvious upon administration of the same active agent to the same subject encompasses by the claims.

Claims 173-177, 179-194, 196-200, 202-203, 205, 206, 231 and 234 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,847,007 of record in view of Chander et al. (1991) of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent disclose and teach an aspect of the claims in the present application. Both sets of claims encompass administration of the same active agent (a structural analog of tamoxifen) to the same subject (a mammal at risk of or afflicted with a cardiovascular or vascular indication such as atherosclerosis) for purpose of increasing TGF-beta level. The patent does not expressly teach the specific tamoxifen analog (i.e. idoxifene), however, the employment of a structural analog of tamoxifen such as idoxifene would have been obvious variations of the other to one of ordinary skill in the art since it is well known in view Chander et al. that idoxifene (pyrrolidino-4-iodotomoxifen) is a new analogue of tamoxifen (see title).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 173-175, 177,179-181,196-200, 203, 205, 206 and 231 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 1992).

Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats.

Sawada et al. do not teach a mammal at risk of or afflicted with cardiovascular or vascular indication (atherosclerosis) or mechanism of increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation, and dosage formulation and the employment of analogs set forth in claim 176.

It would have been obvious to one of ordinary skill in the art to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats.

One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration e.g. local, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Further, the reference discloses compounds which have a viable utility and are homolog, isomers or close structural analogs of the claimed compounds. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Claims 173-177, 179-194, 196-199, 205 and 206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang (U.S.Patent No. 5,445,941).

Yang teaches that antiestrogen such as toremifene is useful for treating osteoporosis because it induce human fetal fibroblast to secrete TGFb in absence of estrogen receptor. (column 2, under antiestrogens, column 4, lines 6-10). Yang teaches that elevated serum levels of low density lipoproteins correlate with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction are noted in women with osteoporosis.

It would have been obvious to one of ordinary skill in the art that the osteoporosis patients disclosed by Yang et al. is at risk of cardiovascular or vascular indication characterized by a decreased lumen diameter because a condition such as osteoporosis correlates correlate with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction as taught by Yang et al. With regard to increasing the level of TGF-beta in the osteoporosis patients disclosed by Yang et al. is obvious because Yang et al. teach that toremifene induced secretion of TGB-beta in the absence of estrogen receptor. One of ordinary skill in the art would be motivated to employ toremifene to a patient having osteoporosis disclosed by Yang et al. regardless of their secondary conditions such as diabetes, diabetic retinopathy, or diabetic retinopathy, in order to achieve an expected benefit of inducing secretion of TGF-beta in treating osteoporosis without the estrogen receptor. With regard to employment of idoxifene or doroloxifene are deemed obvious because the cited reference discloses compounds which have a viable utility and toremifene is structural analogs of the

claimed compounds. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties.

Claims 173-177, 179-194, 196-200, 202, 203, 205, 206, 231 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grainger et al. (WO 94/26303) of record in view of Chander et al. of record.

Grainger et al. teach that tamoxifen as well as its functional equivalents, analogs or derivatives thereof are a preferred TGF-beta activator/production stimulator. (page 4, lines 1-5). Grainger et al. teach that these TGF-beta activators and TGF-beta production stimulators are employed to maintain or increase vessel lumen diameter in a diseased or injured vessel of a mammal. (abstract).

Grainger et al. do not teach the employment of the specific structural analog of tamoxifen such as idoxifene.

Chander et al. that idoxifene (pyrrolidino-4-iodotomoxifen) is a new analogue of tamoxifen (see title).

It would have been obvious to one of ordinary skill in the art to employ a structural analogue such as idoxifene for the treatment of a diseases that characterized by a reduced vessel lumen diameter by increasing the level of TGF-beta in a mammal. One would have been motivated to make such a modification because Grainger et al.

teach that tamoxifen as well as its functional equivalents, analogues or derivatives thereof are a preferred TGF-beta activator/production stimulator that are useful in increasing vessel diameter in a diseased or injured vessel of a mammal that is characterized by a reduced vessel lumen diameter and because idoxifene and tamoxifen analogues are a preferred TGF-beta activator/production stimulator of Grainger et al. to treat a reduced vessel lumen diameter in a disease. There is a reasonable expectation of successfully treating a disease characterized by a decreased lumen vessel diameter with idoxifene which is an analog of tamoxifen as a preferred TGF-beta activator/production stimulator as preferred by Grainger et al.

Claims 231 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang (U.S.Patent No. 5, 445,941) of record in view of Frank (1991).

Yang teaches that antiestrogen such as tamoxifen or toremifene secrete TGFb. (column 2, under antiestrogens, column 4, lines 6-10).

Yang does not teach the treatment of diabetic retinopathy with tamoxifen structural analogues.

Frank teaches that the pathogenesis of diabetic retinopathy that several growth factors has been identified in the retina that may promote revascularization, however, that transforming growth-factor b (TGF-b), appears to be an important inhibitor of revascularization. (abstract).

It would have been obvious to one of ordinary skill in the art to employ structural analogues of tamoxifen such as toremifene or idoxifene for the treatment of diabetic

retinopathy because Yang teaches an analogue of tamoxifen such as toremifene secretes TGF-b and that TGF-b is an important inhibitor of revascularization that is involved in the pathogenesis of diabetic retinopathy. The cited reference discloses compounds which have a viable utility and toremifene is structural analogs of the claimed compounds. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. Therefore, one would have been motivated to make such a modification in order to reduce or halt the pathogenesis of diabetic retinopathy by inhibiting revascularization by employment of toremifene or a structural analogues thereof including idoxifene because one of ordinary skill in the art would reasonably also expect the compounds that are so closely related structurally would also secrete TGF-b that is an important inhibitor of revascularization as taught by Frank.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any rejection of record not addressed herein is withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
October 9, 2009